Remarks

Rejection Under 35 U.S.C. § 103

Claims 1, 3, 4, 6-13, 15-23, 25, 26, 34, and 35 were rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 98/46212 to Shah ("Shah"). Applicants respectfully traverse this rejection.

Claim 1 is the only pending independent claim. The claim defines a method ***for micronizing an agent*** (*see e.g.* pages 6-7 of the application), not a method for encapsulation (*see e.g.* pages 8-18 of the application), as follows:

A method for making micronized particles of an agent, comprising:

(a) dissolving a macromolecular material in an effective amount of a solvent, to form a first solution;

(b) dissolving the agent in an effective amount of a solvent, to form a second solution;

(c) adding the second solution to the first solution to form an emulsion and thereby micronize the particles of the agent;

(d) freezing the emulsion;

(e) drying by vacuum the frozen emulsion to form solid micronized particles of the agent dispersed in solid macromolecular material; and

(f) then, dissolving the macromolecular material having dispersed therein solid micronized particles of the agent in an effective amount of a solvent for the macromolecular

material to form a dispersion of solid microparticles of agent in the solvent, wherein the solvent is a non-solvent for the agent.

The examiner's argument is that applicants use of "comprising" in claim 1 means one could make a double emulsion. This ignores the language of the claim. The language requires two solutions, the first of the "macromaterial" and the second of the agent to be micronized, which form an emulsion which is frozen. There is nothing between the language of step c "form an emulsion" and step d "freezing the emulsion", then dissolving the macromaterial, which permits forming a second emulsion. This is strictly a matter of a literal reading of the claim language.

Shah describes a process for encapsulating proteins to form sustained release compositions. The Examiner refers to a working example on page 19. Example 1 begins on page 18 and discloses forming protein loaded microparticles. The microparticles are formed of poly (D,L-lactide-co-glycolide) ("PLGA") and encapsulate the protein, leptin. Shah also discloses *in vitro* tests for the release of leptin from the microparticles. At page 19, line 25, Shah begins describing the *in vitro* release experiment. A 20 mg/mL suspension containing the leptin-PLGA microparticles, 20 mM sodium phosphate (or 20 mM histidine) and 5% Sorbitol at pH 7.4 was formed. At set time intervals, the suspension was centrifuged and leptin concentration of the supernatant was determined using a UV spectrophotometer at 280 nm, and by SEC-HPLC at 220 nm. Shah used this data to determine the amount of leptin released from the PLGA microparticles over time (*see* page 20, lines 2-3 and Figure 2). The leptin dissolves in the

aqueous solvent and leaches out of the matrix.. As shown in the enclosed datasheets from Jena Bioscience GmbH (www.jenabioscience.com) and Absorbable Polymers International (http://www.birminghampolymers.com/tech/Chemical_Properties.asp), leptin is very water soluble, while PLGA is soluble in organic solvents, such as dichloromethane, tetrahydrofuran, ethyl acetate, chloroform, hexafluoroisopropanol, and acetone.

This is the **opposite** of what is claimed!

Applicants require an emulsion, which is frozen to produce a matrix having drug within it; the ***matrix, not the agent***, is dissolved to leave micronized drug particles.

Therefore Shah does not disclose the claimed method.

Additionally, Shah does not suggest following the lyophilization step with a step that dissolves the encapsulating polymer in a solvent to form a dispersion of solid microparticles of agent in the solvent. Such a step defeats the purpose of Shah's entire method, because it would destroy the solid encapsulating material. In contrast, this step is required in claim 1, as pending. Therefore, claims 1, 3, 4, 6-13, 15-23, 25, 26, 34, and 35 are non-obvious in view of Shah.

U.S.S.N. 09/760,046
Filed: January 12, 2001
RESPONSE TO OFFICE ACTION

Allowance of claims 1, 3, 4, 6-13, 15-23, 25, 26, 34, and 35 is respectfully solicited.

Respectfully submitted,

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Chemical Properties of Selected Polymers

A chart of the chemical properties for some of our most used polymers

Polymer Type	Inherent Viscosity (DL/G)	Melting Point (°C)	Glass Transition Temperature (°C)	Solubility At 5% W/W	Approximate Resorption Time (Months)
50/50 DL-PLG	0.55 - 0.75	Amorphous	45 - 50	1,2,3,4,5,6	1 - 2
65/35 DL-PLG	0.55 - 0.75	Amorphous	45 - 50	1,2,3,4,5,6	3 - 4
75/25 DL-PLG	0.55 - 0.75	Amorphous	50 - 55	1,2,3,4,5,6	4 - 5
85/15 DL-PLG	0.55 - 0.75	Amorphous	50 - 55	1,2,3,4,5,6	5 - 6
DL-PLA	0.55 - 0.75	Amorphous	50 - 60	1,2,3,4,5,6	12 - 16
L-PLA	0.90 - 1.2	173-178	60 - 65	1,4,5	>24
PGA	1.4 - 1.8	225-230	35 - 40	5	6 - 12
PCL	1.1 - 1.3	58-63	-65 - -60	1,4,5,6	>24

* Solvents (partial listing only):
1 = dichloromethane
2 = tetrahydofuran
3 = ethyl acetate
4 = chloroform
5 = hexafluoroisopropanol
6 = acetone

Staff Publications

Selected References

Chemical Properties of Selected Polymers

Physical Properties of Selected Polymers

Biodegradation Information

Material Safety Data Material Safety

Absorbable Polymers International
2683 Pelham Parkway
Pelham, AL 35124 USA

Phone: (205) 620-0025
Fax: (205) 620-9888
E-mail:
absorbables@durect.com

Map to API

Absorbable Polymers INTERNATIONAL

A Subsidiary of DIRECT Corporation

ONLINE SALES

Physical Properties of Selected Polymers

A chart of the physical properties for some of our most-used polymers.

Polymer Type	Specific Gravity (G/ML)	Tensile Strength (PSI)	Elongation (%)	Modulus (PSI)
50/50 DL-PLG	1.34	6000 - 8000	3 - 10	$2 - 4 \times 10^5$
65/35 DL-PLG	1.30	6000 - 8000	3 - 10	$2 - 4 \times 10^5$
75/25 DL-PLG	1.30	6000 - 8000	3 - 10	$2 - 4 \times 10^5$
85/15 DL-PLG	1.27	6000 - 8000	3 - 10	$2 - 4 \times 10^5$
DL-PLA	1.25	4000 - 6000	3 - 10	$2 - 4 \times 10^5$
L-PLA	1.24	8000 - 12000	5 - 10	$4 - 6 \times 10^5$
PGA	1.53	10000+	15 - 20	$1 \times 10^{6+}$
PCL	1.11	3000 - 5000	300 - 500	$3 - 5 \times 10^4$

DL-PLG poly(DL-lactide-co-glycolide)
DL-PLA poly(DL-lactide)
L-PLA poly(L-lactide)
PGA poly(glycolide)
PCL poly(ε-caprolactone)

Staff Publications

Selected References

Chemical Properties of Selected Polymers

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Absorbable Polymers INTERNATIONAL

WEB DEVELOPMENT BY INFOMEDIA

Data sheet

▶▶▶ JENA BIOSCIENCE

Leptin
(Obesity Factor)
murine, Recombinant, *E. coli*

Cat.-No.	Amount
PR-481	1 mg

Lyophilized.
Leptin is lyophilized from a 1 mg/ml solution containing 50 mM NH_4HCO_3, pH 8.0.

Leptin inhibits food intake and stimulates energy expenditure. Leptin also has thermogenic actions and regulates enzymes of fatty acid oxidation. Severe hereditary obesity in rodents and humans is caused by defects in leptin production. In addition to its critical role in the physiologic regulation of body weight leptin has a variety of other physiologic and pathologic functions resembling those of cytokines. These functions include the regulation of hematopoiesis, angiogenesis, wound healing, inflammation, and immune responses.

Recombinant Murine Leptin produced in *E. coli* is a single, non-glycosylated, polypeptide chain containing 147 amino acids and having a molecular mass of 16.24 kDa.

Recombinant Leptin is purified by proprietary chromatographic techniques.

AVOID FREEZE/THAW CYCLES.

For in vitro use only!

Solubility: The lyophilized Leptin is very soluble in water and most aqueous buffers below and above the isoelectric point.

Activity: Biological activity of murine Leptin is performed in two different mouse obesity models, ob/ob and NZO. Both strains of mice were treated via intraperitoneal injection once daily at a dose of 5 µg Leptin/gram body weight for a period of 14 days. Significant effects on body weight, food consumption, and plasma glucose levels were observed to saline-treated controls.

Purity: ≥ 97% by SDS-PAGE, RP-HPLC, and FPLC.

Endotoxin: Less than 0.1 ng/µg (IEU/µg) of Leptin.

Store: 4°C

Selected references:
Gaja A. and Chury Z. (2001) [The importance of leptin in oncology—hypothesis or facts?] [Article in Czech] *Vnitr. Lek.* 47:245.
Theriault et al. (2001) Clinical evaluation of a new non-isotopic leptin immunoassay. *Clin. Lab. Sci.* 14:6.
Thomas T. (2004) Leptin and fragility fracture: evidence for a protective effect in humans. *Am. J. Med.* 117:966.
Schett et al. (2004) Serum leptin level and the risk of nontraumatic fracture. *Am. J. Med.* 117:952.
Iwamoto I. and Fujino T. (2004) The leptin receptor in human osteoblasts and the direct effect of leptin on bone metabolism. *Gynecol. Endocrinol.* 19:97.
Mami et al. (2005) Plasma leptin, insulin, and neuropeptide Y concentrations in infants. *Arch. Dis. Child. Fetal. Neonatal. Ed.* 90:F86.

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